Original Article

The efficacy and safety of apatinib in patients with heavily pretreated end-stage cancer: a retrospective study

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Background: Anti-angiogenesis therapy has been a vital treatment option in a variety of cancers. Assessing the efficacy and safety of apatinib in patients with heavily pretreated end-stage cancer is essential.

Methods: Thirty patients with end-stage cancer who were heavily pretreated were enrolled in this study. All patients received oral administration of apatinib (125–500 mg/d) between May 2015 and November 2016. Dose reduction or elevation was conducted based on adverse events and doctors' judgments.

Results: Prior to the apatinib treatment, the enrolled patients received a median of 1.2 surgeries (range, 0–7), 1.6 sessions of radiotherapies (range, 0–6), and 10.2 cycles of chemotherapy (range, 0–60); 43.3% of patients had uncontrolled local lesions, 83.3% of patients had uncontrolled multiple metastases, and 30.0% of patients had both. After the treatment, 25 patients had valuable data, 6 (24.0%) patients achieved partial response (PR), and 12 (48.0%) patients had stable disease (SD). The disease control rate (DCR) was 72.0%. The PR and SD rates were 20.0% and 40.0%, respectively, and the DCR was 60.0% in the intent-to-treat (ITT) analysis. Meanwhile, the median progression-free survival (PFS) was 2.6 (range, 0.7–5.4) months, and the median overall survival (OS) was 3.8 (range, 1.0–12.0) months. Furthermore, the PR rate and DCR in patients with squamous cell cancer (SCC) were 45.5% and 81.8%, respectively; those in patients with adenocarcinoma (ADC) were 8.3% and 58.3%, respectively. The adverse events were generally mild. The most common adverse events were hyperbilirubinemia (53.3%), elevated transaminase (36.7%), anemia (30.0%), thrombocytopenia (30.0%), hematuria (30.0%), fatigue (26.7%), and leukopenia (20.0%).

Conclusions: The results of this study demonstrate the efficacy and safety of apatinib and support the further development of apatinib as a potential treatment option for patients with heavily pretreated end-stage cancer.

Keywords: Apatinib; end-stage cancer; disease control rate (DCR); survival; safety

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Introduction

The characteristics of end-stage cancer, including its high degree of malignancy, treatment resistance, and uncontrollable metastatic lesions, place a large burden on patients (1,2). Various trials have been conducted to explore possible treatments for patients with end-stage cancers. The trials mainly focused on immunotherapies and small molecular inhibitors. However, some treatments are accompanied by uncontrollable adverse effects (3-8). Careful evaluation of the potential benefits and harms of various palliative treatment options is crucial in determining strategies in clinical circumstances (9). The optimal options should be safe, convenient, and tolerable for patients and not simply focus on prolonging the lifespan of patients (10). However, there is no consensus regarding effective palliative treatment except for best supportive care (BSC; including pain release, communication, etc.) for patients with end-stage cancer who desire to live longer. Thus, the development of new therapeutic strategies for these patients is necessary.

Vascular endothelial growth factor (VEGF)-mediated angiogenesis plays a critical role in tumor growth and metastasis (11). Consequently, the targeting of angiogenesis by inhibiting VEGFs is a promising strategy for cancer treatment (12). Several reports have demonstrated the efficacy of this treatment strategy in lung, breast, renal, hepatic, and colon cancers (12-15). Antiangiogenic treatment is also considered one of the potential treatment methods to benefit and increase the survival of patients with cancer and drug resistance, even in those who have been heavily pretreated (16-19).

Apatinib (YN968D1), an oral small-molecular tyrosine kinase inhibitor, selectively targets VEGFR-2 to decrease VEGF-mediated endothelial cell migration, proliferation, and microvascular tumor density (20). Preclinical experiments have indicated that apatinib might be considered a potential therapeutic agent for malignancies and could reverse the resistances to a variety of drugs (21,22). Furthermore, the clinical efficacy of apatinib has been proven in patients with gastric, hepatic, breast, lung, and colorectal cancers (23-29). Furthermore, apatinib is also effective in patients with chemotherapy-refractory or chemotherapy-resistant cancers, such as gastric, breast, and non-small cell lung cancer (NSCLC), who have failed 2 or more previous lines of treatment (30-32).

In this retrospective study, we assessed the clinical efficacy and safety of apatinib in patients with end-stage cancer who had previously received intensive treatment. These patients had uncontrollable local or metastatic lesions and failed or could not tolerate standard therapeutic options. Our analysis might offer new insights into apatinib for overcoming drug resistance and controlling the disease. We present the following article in accordance with the STROBE reporting checklist (available at https://tcr.amegroups.com/article/view/10.21037/tcr-22-2080/rc).

Highlight box

Key findings

- In patients with heavily pretreated end-stage cancer treated with low-dose apatinib, intent-to-treat analysis showed that the partial response and stable disease rates were 20.0% and 40.0%, respectively, with a disease control rate of 60.0%.
- The median progression-free survival was 2.6 months, and the median overall survival was 3.8 months in the entire population.
- The adverse events associated with the low-dose apatinib treatment were generally mild.

What is known and what is new?

- What is known: Recent studies have examined the use of low-dose apatinib monotherapy as a third-line treatment in patients with metastatic colorectal cancer.
- What is new: The treatment with low-dose apatinib was safe and effective in patients with end-stage cancer in a variety of tumors.

What is the implication, and what should change now?

- Low-dose apatinib is a potential treatment option for patients with heavily pretreated end-stage cancer.

Methods

Study design and participants

This study was a retrospective cohort analysis of the best response and survival data collected routinely in patients with end-stage cancer who had previously been heavily treated and who had received low-dose apatinib at the Cancer Center in Union Hospital, Wuhan, China, from May 2015 to November 2016. Thirty patients were enrolled in this study. All patients had uncontrollable progressive lesions, making them unsuitable for surgery, radiotherapy, and chemotherapy (intolerant or progressive disease) after combined chemotherapy). We excluded (I) patients treated with a combination of apatinib and other therapies, such as chemotherapy, radiotherapy, or targeted therapy; and (II) patients who were not at end-stage disease but who had

received mono-apatinib treatment.

Ethical approval

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and was approved by the Institutional Review Board of the Huazhong University of Science and Technology the and Tongji Medical College Ethics Committee for Clinical Investigation (No. 2018S323). Informed consent was obtained from all individual participants.

Apatinib

Patients received oral apatinib at a dose of 125 to 500 mg daily in tablet form and BSC. Dose reductions or elevation were conducted based on adverse events and the diagnosis of the doctor (33). Patients were given continuous treatment until they experienced disease progression or intolerable toxicity.

Outcome evaluation and adverse effects

The response and progression of the disease were evaluated according to the international criteria proposed by the Response Evaluation Criteria in Solid Tumors Committee. The primary end point was the disease control rate (DCR). Disease control was defined as complete response (CR), partial response (PR), or stable disease (SD). In terms of the DCR, whether the patients had CR, PR, or SD in the fourth week of the study was recorded. Secondary end points included progression-free survival (PFS) and overall survival (OS). PFS was defined as the time from the beginning of treatment until disease progression or death, whichever occurred first. OS was defined as the time from treatment until death from any cause or the last follow-up. Toxicity was evaluated according to World Health Organization classification standard of acute and subacute toxicity of anticancer drugs (34).

Statistical analysis

Categorical variables are presented as numbers and percentages. Continuous data are presented as the median with range. Median PFS and OS were estimated with a Kaplan-Meier curve.

Results

Characteristics of the patients

The 30 included patients had a median age of 57 years (range, 28–86 years) were included in this study; of these patients, 10 had head and neck carcinoma, 7 had gynecological cancer, and 13 had digestive cancer. Patients' characteristics are shown in *Table 1*. The average time from the initial pathology diagnosis to the progression of end-stage cancer was 33.4 months (range, 6.6–181.7 months). Patients received a median of 1.2 surgeries (range, 0–7), 1.6 sessions of radiotherapy (range, 0–6), and 10.2 cycles of chemotherapy (range, 0–60) before treatment with apatinib. Additionally, 13 (43.3%) patients had uncontrolled local lesions, 25 (83.3%) patients had uncontrolled multiple metastases, and 9 (30.0%) patients had both local uncontrolled lesions and multiple metastatic sites. The most frequently involved metastatic sites were the bone (14, 46.7%), lungs (12, 40.0%), peritoneum (10, 33.3%), pleura (9, 30.0%), liver (8, 26.7%), and brain (4, 13.3%). Of the patients, 14 (46.7%) were not tolerant to chemotherapy, 14 (46.7%) were refractory or resistant to chemotherapy, and 2 (6.7%) were both (*Table 1*). The detailed clinical characteristics of subgroups, including patients with squamous cell carcinoma (SCC), adenocarcinoma (ADC), uncontrollable local lesion, or uncontrollable metastatic lesion, are also shown in *Table 1*.

Efficacy

Overall, 50% of patients received no more than 250 mg/d of apatinib, and the other 50% of patients received up to 500 mg/d; 5 patients abandoned apatinib therapy within 1 month. Thus, efficacy was evaluated in 25 patients who had valuable data. Of these, 6 (24.0%) patients achieved PR, 12 (48.0%) had SD, and 7 (28.0%) had PD, resulting in an objective response rate (ORR; defined as CR + PR) of 24.0% and a DCR of 72.0%. Median PFS (mPFS) was 2.6 months (range, 0.7–5.4 months), while median OS (mOS) was 3.8 months (range, 1.0–12.0 months) in the entire population (*Table 2*). The PR rate and SD rate were 20.0% and 40.0%, respectively, and the DCR was 60.0% in the intent-to-treat (ITT) analysis.

Efficacy by pathology

Among patients with SCC, 11 patients had valuable data.

Table 1 Characteristics of patients with end-stage cancer

Characteristics	Total patients (n=30)	SCC (n=14)	ADC (n=14)	Local-F (n=13)	Multi-M (n=25)
Age (years), median [range]	57 [28–86]	59 [47–86]	54 [28–60]	60 [47–86]	57 [28–81]
Gender, n (%)					
Male	15 (50.0)	9 (64.3)	5 (35.7)	7 (53.8)	12 (48.0)
Female	15 (50.0)	5 (35.7)	9 (64.3)	6 (46.2)	13 (52.0)
Pathology, n (%)					
SCC	14 (46.7)	14 (100.0)	0 (0.0)	11 (84.6)	9 (36.0)
ADC	14 (46.7)	0 (0.0)	14 (100.0)	1 (7.7)	14 (56.0)
Others*	2 (6.7)	0 (0.0)	0 (0.0)	1 (7.7)	2 (8.0)
Primary tumor, n (%)					
Head and neck cancer	10 (33.3)	9 (64.3)	0 (0.0)	6 (46.2)	6 (24.0)
Gynecological cancer	7 (23.3)	2 (14.3)	5 (35.7)	3 (23.1)	6 (24.0)
Digestive cancer	13 (43.3)	3 (21.4)	9 (64.3)	4 (30.8)	13 (52.0)
Previous treatment					
Average number of surgeries, median (range)	1.2 (0–7)	1.4 (0–7)	1.1 (0–2)	1.5 (0–7)	1.0 (0–3)
Average number of radiotherapy sessions, median (range)	1.6 (0–6)	2.3 (1–6)	1.1 (0–4)	2.2 (1–4)	1.6 (0–6)
Average number of chemotherapy cycles, median (range)	10.2 (0–60)	5.7 (0–18)	15.9 (5–60)	8.9 (0–46)	11.1 (1–60)
Course of disease (months), median (range)	33.4 (6.6–181.7)	22.3 (6.6–59.6)	45.6 (8.3–181.7)	29.5 (6.6–76.6)	36.1 (7.0–181.7)
Local failure after multiline treatment, n (%)	13 (43.3)	11 (78.6)	2 (14.3)	13 (100.0)	8 (25.0)
Tolerance to chemotherapy, n (%)					
No	16 (53.3)	10 (71.4)	6 (42.9)	8 (61.5)	12 (48.0)
Yes	14 (46.7)	4 (28.6)	8 (57.1)	5 (38.5)	13 (52.0)

*, others included sarcoma and ACC. SCC, squamous cell cancer; ADC, adenocarcinoma; ACC, adenoid cystic carcinoma; Local-F, local failure; Multi-M, multiple metastases.

After treatment with apatinib, 5 (45.5%) patients achieved PR, 4 (36.4%) patients had SD, and 2 (18.2%) patients had PD. Therefore, the ORR and DCR were 45.5% and 81.8%, respectively. The mPFS and mOS were 2.1 months (range, 0.7–4.4 months) and 3.7 months (range, 1.0–12.0 months), respectively (*Table 2*).

Among the patients with ADC, 12 patients had valuable data, including 1 (8.3%) patient with PR, 6 (50.0%) patients with SD, and 5 (41.7%) patients with PD. Thus, the ORR and DCR were 8.3% and 58.3%, respectively. The mPFS was 3.0 months (range, 1.8–5.4 months), and the mOS was 4.0 months (range,1.0–7.7 months; *Table 2*). Further comparison analysis revealed that although the ORR was better in patients with SCC compared to those with ADC (45.5% *vs.* 8.3%), no statistical significance was observed (P=0.069), which might be attributable to the small sample size (Table S1).

Efficacy by local failure or multiple metastases

Ten patients had uncontrollable lesions. There were 4 (40.0%) patients with PR, 5 (50.0%) patients with SD, and 1 (10.0%) patient with PD. The ORR and DCR were 40% and 90%, respectively. The mPFS was 2.6 months (range, 0.9–5.2 months), and the mOS was 4.2 months (range, 1.0–12.0 months; *Table 2*).

Table 2 Treatment response and survival profile

Items	Total patients	SCC	ADC	Local-F	Multi-M
Assessed, n	25	11	12	10	22
PR, n (%)	6 (24.0)	5 (45.5)	1 (8.3)	4 (40.0)	3 (13.6)
SD, n (%)	12 (48.0)	4 (36.4)	6 (50.0)	5 (50.0)	12 (54.5)
PD, n (%)	7 (28.0)	2 (18.2)	5 (41.7)	1 (10.0)	7 (31.8)
ORR, n (%)	6 (24.0)	5 (45.5)	1 (8.3)	4 (40.0)	3 (13.6)
DCR, n (%)	18 (72.0)	9 (81.8)	7 (58.3)	9 (90.0)	15 (68.2)
mPFS (months), median (range)	2.6 (0.7–5.4)	2.1 (0.7–4.4)	3.0 (1.8–5.4)	2.6 (0.9–5.2)	2.6 (0.7–5.4)
mOS (months), median (range)	3.8 (1.0–12.0)	3.7 (1.0–12.0)	4.0 (1.0–7.7)	4.2 (1.0–12.0)	3.5 (1.0–7.7)

PR, partial response; SD, stable disease; PD, progressive disease; ORR, objective response rate; DCR, disease control rate; mPFS, median progression-free survival; mOS, median overall survival; SCC, squamous cell carcinoma; ADC, adenocarcinoma; Local-F, local failure; Multi-M, multiple metastases.

Table 3 Treatment response classified by the primary tumor

Outcome	Head and neck cancer	Gynecological cancer	Digestive cancer
Assessed, n	9	5	11
PR, n (%)	3 (33.3)	2 (40.0)	1 (9.1)
SD, n (%)	4 (44.4)	1 (20.0)	7 (63.6)
PD, n (%)	2 (22.2)	2 (40.0)	3 (27.3)
ORR, n (%)	3 (33.3)	2 (40.0)	1 (9.1)
DCR, n (%)	7 (77.7)	3 (60.0)	8 (72.7)

PR, partial response; SD, stable disease; PD, progressive disease; ORR, objective response rate; DCR, disease control rate.

In patients with uncontrollable metastatic lesions, 22 patients had valuable data. Of these, 3 (13.6%) patients achieved PR, 12 (54.5%) patients had SD, and 7 (31.8%) patients had PD, resulting in an ORR and DCR of 13.6% and 68.2%, respectively. The mPFS was 2.6 months (range, 0.7–5.4 months), and the mOS was 3.5 months (range, 1.0–7.7 months; *Table 2*).

Efficacy by primary tumor site

In patients with head and neck cancer, there were 3 (33.3%) patients with PR, 4 (44.4%) patients with SD, and 2 (22.2%) patients with PD, which resulted in an ORR of 33.3% and a DCR of 77.7%. In patients with gynecological cancer, 2 (40.0%) patients achieved PR, 1 (20.0%) patient had SD, and the other 2 (40.0%) patients had PD. The ORR and DCR were 40.0% and 60.0%, respectively. In patients with digestive cancer, 1 (9.1%) patient achieved PR, 7 (63.6%) patients had SD, and 3 (27.3%) patients had PD. The ORR and DCR were 9.1% and 72.7%, respectively (*Table 3*).

Safety

Major observed toxicities of low-dose apatinib included hyperbilirubinemia (16 patients, 53.3%), elevated transaminase (11 patients, 36.7%), anemia (9 patients, 30.0%), thrombocytopenia (9 patients, 30.0%), hematuria (9 patients, 30.0%), fatigue (8 patients, 26.7%), and leukopenia (6 patients, 20.0%; *Table 4*). Most of the toxicities were of grades 1–2. The most common grades 3–4 toxicities were thrombocytopenia (5 patients, 16.7%) and hyperbilirubinemia (3 patients, 10.0%; *Table 4*).

Each patient's specific disease, apatinib administration, treatment response, survival, and grades 3–4 adverse events are listed in Table S2 for reference.

Discussion

Our results illustrated that low-dose apatinib was a potentially effective anticancer agent with an acceptable safety profile that could be used for heavily pretreated patients with end-stage cancers or patients with uncontrollable lesions who failed or were not tolerant to chemotherapy. To the best of our knowledge, this was the first study of cancer patients who had received low-dose apatinib in the final stage of their lives. Notably, it also reported apatinib treatment in head and neck

Table 4 Adverse events

Adverse events	Total	Grades 1–2	Grades 3–4
Hyperbilirubinemia, n (%)	16 (53.3)	13 (43.3)	3 (10.0)
Elevated transaminase, n (%)	11 (36.7)	10 (33.3)	1 (3.3)
Anemia, n (%)	9 (30.0)	7 (23.3)	2 (6.7)
Thrombocytopenia, n (%)	9 (30.0)	4 (13.3)	5 (16.7)
Hematuria, n (%)	9 (30.0)	9 (30.0)	0 (0.0)
Fatigue, n (%)	8 (26.7)	6 (20.0)	2 (6.7)
Leukopenia, n (%)	6 (20.0)	4 (13.3)	2 (6.7)
Hand-foot syndrome, n (%)	5 (16.7)	4 (13.3)	1 (3.3)
Hypertension, n (%)	4 (13.3)	4 (13.3)	0 (0.0)
Proteinuria, n (%)	3 (10.0)	3 (10.0)	0 (0.0)
Bleeding, n (%)	3 (10.0)	3 (10.0)	0 (0.0)

squamous cancers, esophageal squamous cell carcinoma, nasopharyngeal carcinoma, non-breast gynecological cancers, and adenoid cystic carcinoma. Among 13 cases, 5 PR, 6 SD, and 2 PDs were observed, and both patients with nasopharyngeal carcinoma showed PD disease. This study also suggested that apatinib had a better effect on SCC.

Several studies support the idea that apatinib may be effective in multiline-failed and end-stage patients who are chemo-refractory or have a high degree of malignancy or resistance. In a randomized controlled phase III trial of 267 patients with advanced gastric cancer who failed in the second-line chemotherapy, patients who were treated with apatinib (750 mg/d) achieved a DCR of 42.1% and an mPFS of 2.6 months; in the placebo group, the DCR was 8.8%, and the mPFS was 1.8 months (32). A possible reason for these findings could be that a high dose of apatinib might be intolerable in these patients, and they postponed apatinib administration, which might have led to poor survival. A phase II, multicenter, open, single-arm clinical study that included 36 patients with metastatic breast cancer for whom chemotherapy had failed and who were treated with apatinib (500 mg/d) reported an ORR of 16.7%, a DCR of 66.7%, and an mPFS of 4.0 months (35). This study pooled different types of end-stage cancer and obtained a DCR of 72%, an ORR of 24%, and an mPFS of 2.7 months, similar to the findings of the above-mentioned clinical trials (32,35). These results showed that even with low-dose apatinib (125–500 mg/d), effective outcomes could still be achieved, providing evidence for reducing the drug dose in clinical treatment for patients with multiline failure and/or end-stage cancer.

Previous studies on the adverse events of apatinib have mainly focused on hypertension, hand-food syndrome, proteinuria, diarrhea, fatigue, and leukopenia (27,36-38). Most of published literature indicates that grade 3–4 adverse events rarely occur. In our study, the common adverse events were similar to those previously reported. Most of the adverse events were tolerable and manageable. Our study further indicated that apatinib could be a safe treatment in patients with end-stage cancer or patients with uncontrollable lesions who were not tolerant to chemotherapy or for whom chemotherapy had failed.

This study also evaluated the efficacy of apatinib in SCC and ADC. According to the published literature, in patients with previously treated SCC who had received apatinib treatment, the ORR ranged from 7.5% to 12.5%, while the DCR ranged from 65.0% to 72.5% (36-38). However, studies using apatinib monotherapy in patients with previously treated ADC are rare. Only one study was conducted on colorectal cancer, reporting a DCR of 23.0% (27). In our study, the ORR of low-dose apatinib in patients with ADC or SCC was 8.3% and 45.5%, respectively, and DCR with ADC or SCC was 58.3% and 81.8%, respectively. The treatment response in patients with SCC was similar to that previously reported. From our data, it could be observed that the treatment response was better in patients with SCC compared to patients with ADC. Thus, we propose that patients with SCC might be more sensitive to apatinib treatment compared to patients with ADC. Therefore, further randomized clinical studies are highly recommended to assess the use of low-dose apatinib in patients with SCC.

The results of this study show that a low-dose of apatinib (125–500 mg/day) also exerted effective antitumor activity. Previously, high and unacceptable toxicity was observed in patients with a standard dose of apatinib treatment. In a phase II trial of metastatic breast cancer, the apatinib dose was reduced from 750 to 500 mg/day due to the unacceptable toxicity of the 750 mg/day dose (31). A low-dose of apatinib was shown to be effective. A phase I clinical trial reported that, in 37 patients with gastrointestinal, bronchus/lung, breast, and other cancers treated with oral apatinib at a dose ranging from 250 to 1,000 mg/day, the DCR of the 250, 500, 750, 850, 1,000 mg dose cohorts was 66.7%, 66.7%, 100.0%, 90.9%, and 66.7%, respectively (39). Thus, it is worth investigating the efficacy and toxicity of apatinib at lower doses in patients with end-stage cancer. In patients with end-stage cancer, the balance

of adverse events and survival benefits should be considered. In the current study, a low dose of apatinib was effective and tolerable, and thus might be a potential choice for patients with end-stage cancer (40,41).

This study has some limitations. First, there was no randomized, double-blind control group that received a placebo compared with low-dose apatinib. Second, the sample size of this study was insufficiently large to draw definitive conclusions. Third, studies on different aspects of quality of life should also be included. Fourth, the quality of life was not evaluated in this study. Fifth, we enrolled patients with various types of end-stage cancer, including head and neck cancer, gynecological cancer, breast cancer and digestive cancer, which might have confounded the results. Further studies should consider these limitations to verify the conclusions.

Conclusions

Collectively, apatinib can be administered as an alternative monotherapy with a high DCR and moderate adverse events in patients with heavily pretreated end-stage cancer. As low-dose apatinib yielded a good response in patients with SCC, it is worth further investigating its therapeutic effects in this specific group.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://tcr.amegroups.com/article/view/10.21037/tcr-22-2080/rc

Data Sharing Statement: Available at https://tcr.amegroups.com/article/view/10.21037/tcr-22-2080/dss

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tcr.amegroups.com/article/view/10.21037/tcr-22-2080/coif). The authors have no potential conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the Institutional Review Boards of the Huazhong University of Science and Technology, and Tongji Medical College Ethics Committee for Clinical Investigation (No. 2018S323), and informed consent was obtained from all individual participants.

References

1. Fares J, Fares MY, Khachfe HH, et al. Molecular principles of metastasis: a hallmark of cancer revisited. Signal Transduct Target Ther 2020;5:28.
2. Cindy Yang SY, Lien SC, Wang BX, et al. Pan-cancer analysis of longitudinal metastatic tumors reveals genomic alterations and immune landscape dynamics associated with pembrolizumab sensitivity. Nat Commun 2021;12:5137.
3. Tolaney SM, Barroso-Sousa R, Keenan T, et al. Effect of Eribulin With or Without Pembrolizumab on Progression-Free Survival for Patients With Hormone Receptor-Positive, ERBB2-Negative Metastatic Breast Cancer: A Randomized Clinical Trial. JAMA Oncol 2020;6:1598-605.
4. Glisson BS, Leidner RS, Ferris RL, et al. Safety and Clinical Activity of MEDI0562, a Humanized OX40 Agonist Monoclonal Antibody, in Adult Patients with Advanced Solid Tumors. Clin Cancer Res 2020;26:5358-67.
5. Lheureux S, Oaknin A, Garg S, et al. EVOLVE: A Multicenter Open-Label Single-Arm Clinical and Translational Phase II Trial of Cediranib Plus Olaparib for Ovarian Cancer after PARP Inhibition Progression. Clin Cancer Res 2020;26:4206-15.

6. Kang YK, Bang YJ, Kondo S, et al. Safety and Tolerability of Bintrafusp Alfa, a Bifunctional Fusion Protein Targeting TGFβ and PD-L1, in Asian Patients with Pretreated Recurrent or Refractory Gastric Cancer. Clin Cancer Res 2020;26:3202-10.
7. Moore KN, Secord AA, Geller MA, et al. Niraparib monotherapy for late-line treatment of ovarian cancer (QUADRA): a multicentre, open-label, single-arm, phase 2 trial. Lancet Oncol 2019;20:636-48.
8. Dhar R, Seethy A, Singh S, et al. Cancer immunotherapy: Recent advances and challenges. J Cancer Res Ther 2021;17:834-44.
9. Randén M, Helde-Frankling M, Runesdotter S, et al. Treatment decisions and discontinuation of palliative chemotherapy near the end-of-life, in relation to socioeconomic variables. Acta Oncol 2013;52:1062-6.
10. Prigerson HG, Bao Y, Shah MA, et al. Chemotherapy Use, Performance Status, and Quality of Life at the End of Life. JAMA Oncol 2015;1:778-84.
11. Khodabakhsh F, Merikhian P, Eisavand MR, et al. Crosstalk between MUC1 and VEGF in angiogenesis and metastasis: a review highlighting roles of the MUC1 with an emphasis on metastatic and angiogenic signaling. Cancer Cell Int 2021;21:200.
12. Yi M, Jiao D, Qin S, et al. Synergistic effect of immune checkpoint blockade and anti-angiogenesis in cancer treatment. Mol Cancer 2019;18:60.
13. Nakagawa K, Garon EB, Seto T, et al. Ramucirumab plus erlotinib in patients with untreated, EGFR-mutated, advanced non-small-cell lung cancer (RELAY): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol 2019;20:1655-69.
14. Vasseur A, Cabel L, Tredan O, et al. Prognostic value of CEC count in HER2-negative metastatic breast cancer patients treated with bevacizumab and chemotherapy: a prospective validation study (UCBG COMET). Angiogenesis 2020;23:193-202.
15. Fuchs CS, Shitara K, Di Bartolomeo M, et al. Ramucirumab with cisplatin and fluoropyrimidine as first-line therapy in patients with metastatic gastric or junctional adenocarcinoma (RAINFALL): a double-blind, randomised, placebo-controlled, phase 3 trial. Lancet Oncol 2019;20:420-35.
16. Shoji T, Enomoto T, Abe M, et al. Efficacy and safety of standard of care with/without bevacizumab for platinum-resistant ovarian/fallopian tube/peritoneal cancer previously treated with bevacizumab: The Japanese Gynecologic Oncology Group study JGOG3023. Cancer Sci 2022;113:240-50.
17. Sjoquist KM, Espinoza D, Mileshkin L, et al. REZOLVE (ANZGOG-1101): A phase 2 trial of intraperitoneal bevacizumab to treat symptomatic ascites in patients with chemotherapy-resistant, epithelial ovarian cancer. Gynecol Oncol 2021;161:374-81.
18. Takemoto S, Nakamura Y, Gyoutoku H, et al. Phase II trial of a non-platinum triplet for patients with advanced non-small cell lung carcinoma (NSCLC) overexpressing ERCC1 messenger RNA. Thorac Cancer 2019;10:452-8.
19. Mizushima T, Fukunaga M, Sueda T, et al. Phase I/II study of bi-weekly XELIRI plus bevacizumab treatment in patients with metastatic colorectal cancer resistant to oxaliplatin-based first-line chemotherapy. Cancer Chemother Pharmacol 2017;80:81-90.
20. Tian Z, Niu X, Yao W. Efficacy and Response Biomarkers of Apatinib in the Treatment of Malignancies in China: A Review. Front Oncol 2021;11:749083.
21. Tian S, Quan H, Xie C, et al. YN968D1 is a novel and selective inhibitor of vascular endothelial growth factor receptor-2 tyrosine kinase with potent activity in vitro and in vivo. Cancer Sci 2011;102:1374-80.
22. Mi YJ, Liang YJ, Huang HB, et al. Apatinib (YN968D1) reverses multidrug resistance by inhibiting the efflux function of multiple ATP-binding cassette transporters. Cancer Res 2010;70:7981-91.
23. Ren D, Wang G, Zhang Y, et al. Efficacy and Safety of Apatinib for Elderly Patients with Advanced or Metastatic Gastric Cancer After Failure of at Least First-Line Chemotherapy: A Multi-Center, Single-Arm, Phase II Study. Onco Targets Ther 2021;14:4499-508.
24. Qin S, Li Q, Gu S, et al. Apatinib as second-line or later therapy in patients with advanced hepatocellular carcinoma (AHELP): a multicentre, double-blind, randomised, placebo-controlled, phase 3 trial. Lancet Gastroenterol Hepatol 2021;6:559-68.
25. Liu J, Liu Q, Li Y, et al. Efficacy and safety of camrelizumab combined with apatinib in advanced triple-negative breast cancer: an open-label phase II trial. J Immunother Cancer 2020;8:e000696.
26. Zhao H, Yao W, Min X, et al. Apatinib Plus Gefitinib as First-Line Treatment in Advanced EGFR-Mutant NSCLC: The Phase III ACTIVE Study (CTONG1706). J Thorac Oncol 2021;16:1533-46.
27. Chen X, Qiu T, Zhu Y, et al. A Single-Arm, Phase II Study of Apatinib in Refractory Metastatic Colorectal Cancer. Oncologist 2019;24:883-e407.

28. Li Y, Li HL, Hu HT, et al. Clinical observation of local intervention combined with camrelizumab and apatinib in the treatment of metastatic soft-tissue sarcoma. J Cancer Res Ther 2021;17:1718-24.
29. Shen L, Chen S, Qiu Z, et al. Transarterial chemoembolization combined with apatinib versus transarterial chemoembolization alone for hepatocellular carcinoma with macroscopic vascular invasion: A propensity score matching analysis. J Cancer Res Ther 2020;16:1063-8.
30. Wu F, Zhang S, Xiong A, et al. A Phase II Clinical Trial of Apatinib in Pretreated Advanced Non-squamous Non-small-cell Lung Cancer. Clin Lung Cancer 2018;19:e831-42.
31. Hu X, Zhang J, Xu B, et al. Multicenter phase II study of apatinib, a novel VEGFR inhibitor in heavily pretreated patients with metastatic triple-negative breast cancer. Int J Cancer 2014;135:1961-9.
32. Brower V. Apatinib in treatment of refractory gastric cancer. Lancet Oncol 2016;17:e137.
33. Yuan S, Fu Q, Zhao L, et al. Efficacy and Safety of Apatinib in Patients with Recurrent or Refractory Melanoma. Oncologist 2022;27:e463-e470. Erratum in: Oncologist 2022. PMID: 35348754; PMCID: PMC9177116.
34. Niu YD, Zhang YW, Zhu RJ, et al. The influence of various myelosuppression degrees during neoadjuvant chemotherapy on the curative effect and prognosis of triple-negative breast cancer. Zhonghua Yi Xue Za Zhi 2022;102:2290-4.
35. Hu X, Cao J, Hu W, et al. Multicenter phase II study of apatinib in non-triple-negative metastatic breast cancer. BMC Cancer 2014;14:820.
36. Chu L, Chen Y, Liu Q, et al. A Phase II Study of Apatinib in Patients with Chemotherapy-Refractory Esophageal Squamous Cell Carcinoma (ESO-Shanghai 11). Oncologist 2021;26:e925-35.
37. Geng Q, Shen H, Zhu W, et al. Safety and Efficacy of Low-Dosage Apatinib Monotherapy in Advanced Lung Squamous-Cell Carcinoma: A Prospective Cohort Study. Onco Targets Ther 2020;13:11529-35.
38. Liu G, Wang Y, Wang C, et al. Clinical efficacy and safety of apatinib as maintenance treatment in patients with advanced esophageal squamous cell carcinoma. Expert Rev Clin Pharmacol 2020;13:1423-30.
39. Li J, Zhao X, Chen L, et al. Safety and pharmacokinetics of novel selective vascular endothelial growth factor receptor-2 inhibitor YN968D1 in patients with advanced malignancies. BMC Cancer 2010;10:529.
40. Zeng T, Sun C, Liang Y, et al. A Real-World Multicentre Retrospective Study of Low-Dose Apatinib for Human Epidermal Growth Factor Receptor 2-Negative Metastatic Breast Cancer. Cancers (Basel) 2022;14:4084.
41. Zhao L, Yu Q, Gao C, et al. Studies of the Efficacy of Low-Dose Apatinib Monotherapy as Third-Line Treatment in Patients with Metastatic Colorectal Cancer and Apatinib's Novel Anticancer Effect by Inhibiting Tumor-Derived Exosome Secretion. Cancers (Basel) 2022;14:2492.

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